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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/515,513	02/29/2000	Wu Bo Li	0942.4870001/RWE	1139

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/515,513	LI ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- Th MAILING DATE of this communication app ars on th cover sh et with th correspond nce addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *47-63,106 and 107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-50,53-63 and 106* is/are rejected.

7)☒ Claim(s) *51,52 and 107* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 47-63, 106 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 47 is indefinite with respect to the phrase "one or more cDNA molecules or a population of cDNA molecules" (emphasis added). Claims 48-63 and 106-107, which depend from claim 47, fail to overcome this issue and are similarly rejected.

Response to argument

At page 4 of the response received 13 May 2003, hereinafter the response, it is asserted:

> Both excerpts show that the term "population" is used to describe a group of nucleic acid molecules suitable for the production of a cDNA library, a meaning that is routinely applied to the term by persons of ordinary skill in the art. By contrast, the term "one or more cDNA molecules" includes a potentially low number of different nucleic acid molecules. Thus, the specification provides a clear distinction between the terms "one or more cDNA molecules" and "a population of cDNA molecules." Therefore, Applicants respectfully request that the rejection of claim 47 under 35 U.S.C. § 1 12, second paragraph, be withdrawn. (Emphasis added)

The above argument has been fully considered and has not been found dispositive of the issue such that the rejection of claim 47, and claims48-63, 106, and 107,which depend therefrom, is withdrawn. It is noted with particularity that the term "population" is not used in context of "a group of nucleic acid molecules suitable for the production of a cDNA library," but rather, is used to describe an actual "population of cDNA molecules." Further, while applicant asserts that

the phrase "one or more cDNA molecules" includes a "potentially low number," there is no lower limit set for the "population." Accordingly, it is not clear how the "population" is any different from "one or more cDNA molecules."

4. Claims 47, 52, and 53 are indefinite with respect to the differences that exist between "reduce or substantially reduce."

Response to argument

5. At page 4, bridging to page 5, applicant asserts that "reduced" is to be interpreted as "lessened." Applicant also reproduces a definition for "substantially reduced RNase H activity."

6. While agreement is reached in that the specification provides a definition for "substantially reduced in RNase H activity," the definition does not allow for clear demarcation between what constitutes the limit of the range encompassed by "substantially reduced" as compared to that of "reduced," when as here, they are both being used in the same claim. In particular, if the "substantially" can range from "less than 30%" to "less than 2%." Where does "reduced" fall within or without this range?

7. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

8. The term "low" in claim 50 is a relative term that renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

Response to argument

9. At page 6 of the response applicant asserts:

> The term "low" in claim 50 refers to the temperature at which an inhibitor of the currently-claimed invention inhibits reverse transcriptase activity. Applicants respectfully direct the Examiner's attention to the following passage in the specification:
>
> > Such reverse transcriptase inhibitors prevent or inhibit reverse transcriptase activity *at low temperatures* such that internal priming is prevented, inhibited, reduced or substantially reduced. In accordance with the invention, such inhibitors preferably prevent reverse transcriptase activity below 35°C, below 40°C, below 45°C, below 50°C, below 55°C, below 60°C, below 65°C, below 70°C, below 75°C, below 80°C, below 85°C and below 90°C. Depending on the thermostability of the enzyme having reverse transcriptase activity, the inhibitor may be designed to inhibit activity of the enzyme at a point at or near the temperature optimum. Specification at 7 (emphasis added).

10. The above argument has been fully considered and has not been found persuasive, as the definition is non-binding. In particular, the definition does not set limits, but instead provides yet other open-ended ranges of preferred embodiments.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 47-63 and 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scalice et al. (US Patent 5,338,671), in view of Myers et al. (*Biochemistry*), Clonetech, and Odawara (US Patent 5,989,819).

15. For convenience, claim 47, the only independent claim, is reproduced below.

47. (Once amended) A method for synthesizing one or more cDNA molecules or a population of cDNA molecules, comprising mixing at least one mRNA template, poly A RNA template or population of such templates with at least one polypeptide having reverse transcriptase activity and an inhibitor of the polypeptide having reverse transcriptase activity, under conditions that inhibit, prevent, reduce or substantially reduce the synthesis of non-specific cDNA products when compared to when said inhibitor is absent, and synthesizing one or more cDNA molecules or a population of cDNA molecules.

16. For purposes of examination, the claims have been interpreted as encompassing the production of cDNA molecules from either RNA or from prior cDNA through an amplification reaction such as PCR.

17. The phrase "polypeptide having reverse transcriptase activity" has been interpreted as encompassing any molecule that can exhibit such activity, and that the activity need not be continually present. The aspect of "conditions that inhibit, prevent or reduce the synthesis of non-specific cDNA products" has been interpreted as encompassing any condition that would result in said reduction, even where the reduction is not statistically significant.

18. For convenience, claim 51 has been reproduced below.

51. The method of claim 47, wherein said polypeptide is a reverse transcriptase selected from the group consisting of M-MLV RT, RSV RT, AMV RT, RAV RT, MAV RT and HIV RT, and derivatives, fragments, mutations and variants thereof.

19. The aspect of "derivatives, fragments, mutations and variants" has been interpreted as encompassing virtually any and every polypeptide that exhibits reverse transcriptase activity. Such polypeptides can also be recognized as possessing additional activities, including but not limited to DNA polymerase activity.

20. Scalice et al., teach performing amplification reactions where antibodies bind to the polymerase at a low temperature and thereby inactivate it (column 7). At column 4, last two paragraph, Scalice et al., teach that the starting material can be DNA or RNA, and can be purified or not, and that the specimen from which the sample is derived can be of virtually any source,

21. Scalice et al., column 6, discloses preferred embodiments for primers- that they can range from 12 to 60 nucleotides and preferably 18 to 45 nucleotides. In comparison, applicant preferred primers range in size from 20 to 100, and "still more preferably greater than about 30 bases" (specification at page 4, line 19).

22. Scalice et al., column 9, penultimate paragraph, teaches of the production and use of antibodies that bind to DNA polymerases. Specifically taught are the use of antibodies TP2, TP4, TP5, and TP8, which "have high affinity for . . . *Thermus thermophilus* DNA polymerase."

23. Scalice et al., do not disclose the DNA polymerase from *Thermus thermophilus* as having reverse transcriptase activity.

24. Myers et al., abstract, teach explicitly that the DNA polymerase from *Thermus thermophilus* is *Tth*, and that this "DNA polymerase" also "possess[es] very efficient reverse transcriptase (RT) activity in the presence of $MnCl_2$."

25. Clonetech disclose the commercial availability of antibodies that inhibit the polymerase activity of *Tth* and that such are effective in inhibiting polymerase activity during set-up (low temperature) of PCR reactions.

26. Odawara disclose the identification of antibodies that have an inhibitory effect on reverse transcriptases and that such have been used in assays using a poly-A RNA template.

27. In view of the teachings of the prior art of record, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to applied the method of Scalice et al., where *Tth* polymerase was used in an amplification reaction, in combination with inhibitory antibodies that bind to said polymerase where said *Tth* polymerase is sued in a manner that capitalizes upon its DNA polymerase activity. It would have also been obvious to have modified the method of Scalice et al., with that of Myers et al., whereby said cDNA is synthesized with said *Tth* polymerase under conditions where said polymerase exhibits reverse transcriptase activity for as shown by Myers et al., *Tth* polymerase is also a "very efficient reverse transcriptase." Said artisan would have been motivated to have employed inhibitory anti-*Tth* antibodies as disclosed by Scalice et al., as such has been shown to reduce non-specific priming. Also, said ordinary artisan would have been motivated to have used anti-*Tth* antibodies which act on said polymerase when such is exhibiting reverse transcriptase activity as the protein is the same and the Scalice et al., and Odawara have shown that inhibitory antibodies can be produced against proteins that exhibit either DNA polymerase activity and/or reverse transcriptase activity (including reverse transcriptase of viral origin (Odawara)).

28. While the prior art does not teach the specific concentrations or ratios, such is not considered to constitute a non-obvious embodiment, but rather, are the result of routine experimentation. It is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in

> degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

29. For the above reasons, and in the absence of convincing evidence to the contrary, the claimed invention is rejected under 35 USC 103(a).

Response to argument

30. At pages 7-12 of the response argument is advanced that the prior art does not fairly teach the claimed invention and that the prior art lacks motivation to combine even if the prior art could be combined. Particular attention is directed to the alleged aspect of the prior art not teaching or suggesting that an antibody against *Tth* would be inhibitory of reverse transcriptase activity (page 8, last paragraph, bridging to page 9 of the response).

31. The above argument has been fully considered and has not been found persuasive. Careful consideration of the claim language reveals that while the protein exhibiting reverse transcriptase activity is to be mixed with an "inhibitor ... under conditions that inhibit, prevent, reduce or substantially reduce the synthesis of non-specific cDNA products," there is no requirement that the "inhibitor" actually inhibit reverse transcriptase activity. As shown above, *Tth* is in one instance, or set of reaction conditions, a DNA polymerase, yet it is also a "very

efficient" reverse transcriptase (Myers et al.). Scalice et al., teach explicitly of producing not one but four different monoclonal antibodies that not only bind with "high affinity" to *Tth*, but also demonstrate an ability to inhibit same at low temperatures.

32. Accordingly, the prior art, in contrast to applicant's assertions, does teach such an antibody, and provides ample motivation for their use as well as a most reasonable expectation of success as multiple antibodies have been produced that exhibit such activity. To the extent that the polypeptide is used under conditions whereby it exhibits reverse transcriptase activity, Scalice et al., clearly teach that their antibodies bind to said protein, and Odawara also teaches the production of antibodies that bind to not just any reverse transcriptase, but to those that are of viral origin.

33. Therefore, in view of the above arguments, the teachings of the prior art, and the absence of convincing evidence to the contrary, the rejection is maintained against claims 47-63 and is also applied against new claims 106 and 107.

Conclusion

34. Rejections and/or objections that appeared in the prior Office action and which were not repeated hereinabove have been withdrawn.

35. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

36. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

38. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

39. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
18 November 2003